961

Bohn, Brent

From: Lee, Janice
Sent: Tuesday, June 24, 2014 1:23 PM
To: Powers, Christina
Subject: FW: ICCVAM Working Group on Arsenic Toxicity

Here's the info I was telling you about. Looks like this is part of niehs/ntp?
Interesting.....

From: Cowden, John
Sent: Wednesday, June 04, 2014 3:58 PM
To: Lowit, Anna; Sams, Reeder
Cc: Lee, Janice
Subject: RE: ICCVAM Working Group on Arsenic Toxicity

Hi Anna,

Happy Wednesday! I hope that things are going well for you today.

Thanks for the heads up! We would definitely be interesting in hearing about this work.

Have a great afternoon!

John

John Cowden, Ph.D.
Hazardous Pollutant Assessment Group (HPAG)
National Center for Environmental Assessment (NCEA)
U.S. Environmental Protection Agency - RTP
(919) 541-3667

From: Lowit, Anna
Sent: Wednesday, June 04, 2014 3:52 PM
To: Sams, Reeder; Cowden, John
Subject: Fw: ICCVAM Working Group on Arsenic Toxicity

Hey guys

Have u seen this?

From: Neepa Choksi <nchoksi@ils-inc.com>
Sent: Wednesday, June 04, 2014 3:27:35 PM
To: McCarroll, Nancy; diego.rua@fda.hhs.gov; jmatheson@cpsc.gov; Suzanne.Fitzpatrick@fda.hhs.gov; mgm4@CDC.GOV; Lowit, Anna; Elizabeth Maull; Warren Casey
Cc: Dave Allen; Brett Jones
Subject: ICCVAM Working Group on Arsenic Toxicity

Hello --

As a follow up to the last ICCVAM meeting, I am contacting you based on your expressed interest in participating in an ICCVAM agency working group that will focus on developing adverse outcome pathways for arsenic toxicity. Given the widespread interagency interest in arsenic toxicity, this group will provide a forum to collaborate and gather information needed to build AOPs for the multiple health effects associated with exposure to arsenic. We'd like to convene an organizational teleconference to begin this dialog and establish a focus and charge for the group. With that in mind, you should receive an invitation from Meeting Wizard shortly with proposed dates and times for the teleconference.

Teleconference connection information and a meeting agenda will be forwarded prior to the meeting. As previously indicated, if you believe that there are other individuals that would be interested in participating on this group, please let me know and I will include them on future distributions.

Please feel free to contact me with any questions or concerns.

Sincerely,
Neepa Choksi

Neepa Y. Choksi, Ph.D.
Senior Toxicologist
Integrated Laboratory Systems, Inc.
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RTP, NC 27709
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(919) 544-5091 (fax)
nchoksi@ils-inc.com
www.ils-inc.com

962

Bohn, Brent

From: Powers, Christina
Sent: Tuesday, June 24, 2014 1:14 PM
To: Lee, Janice
Cc: Powers, Christina
Subject: Vascular MOA info
Attachments: 2014 06 05 MOA Table Vascular Remodeling - draft_CP2.docx; 2014 06 05 Hypothesized MOA Vascular Mechanisms_CP2.docx

Hey Janice,

Attached is the draft table and summary of vascular MOA information that Lauren and John have been working on. There are a multitude of track changes included so it's probably easier to look at it with "no changes showing".

Let me know if any other info would be helpful!

Cheers,
Christy

Bohn, Brent

977

From: Jones, Ryan
Sent: Monday, July 28, 2014 4:49 PM
To: Powers, Christina; Lee, Janice; Cowden, John
Subject: RE: iAs MOA lit search
Attachments: MOA tags.xlsx; 2014 04 09 iAs Susceptibility for MOA Literature Categorization (2).docx; 2014 04 03 iAs MOA Literature Categorization (3).docx

These are the files I was given for keywords

From: Powers, Christina
Sent: Monday, July 28, 2014 2:22 PM
To: Jones, Ryan; Lee, Janice; Cowden, John
Cc: Powers, Christina
Subject: iAs MOA lit search

Hi Ryan,

Thanks so much for your helpful insight during today's call discussing the mode of action lit search. Would you mind sending all of the keyword lists that you've tagged the MOA cluster with? I just want to double-check how they align and make sure I'm correctly identifying the lists that you received from John, myself and Janice.

Thanks!!
Christy

Christy Powers
Biologist
National Center for Environmental Assessment (B 220-I)
Office of Research and Development
U.S. Environmental Protection Agency
Ann Arbor, MI

Tel: 734.214.4243
E-mail: powers.christina@epa.gov

980

Bohn, Brent

From: Joca, Lauren
Sent: Monday, July 28, 2014 2:57 PM
To: Powers, Christina
Subject: I've updated the permissions on my shared calendar

Microsoft Exchange Calendar:

Joca, Lauren - iAs AOP Team Action Items
Joca, Lauren (Joca.Lauren@epa.gov) has invited you to view his or her "iAs AOP Team Action Items" calendar.

Joca, Lauren (Joca.Lauren@epa.gov) has invited you to view his or her 'iAs AOP Team Action Items' Calendar.

For instructions on how to view shared folders on Exchange, see the following article:

~~*~*~*~*~*~*~*~*

983

Bohn, Brent

From: Joca, Lauren
Sent: Monday, July 28, 2014 2:29 PM
To: Powers, Christina
Subject: I'd like to share my calendar with you

Microsoft Exchange Calendar:

Joca, Lauren - iAs AOP Team Action Items
Joca, Lauren (Joca.Lauren@epa.gov) has invited you to view his or her "iAs AOP Team Action Items" calendar.

Joca, Lauren (Joca.Lauren@epa.gov) has invited you to view his or her 'iAs AOP Team Action Items' Calendar.

For instructions on how to view shared folders on Exchange, see the following article:

~~*~*~*~*~*~*~*~*~*

984

Bohn, Brent

From: Powers, Christina
Sent: Monday, July 28, 2014 2:22 PM
To: Jones, Ryan; Lee, Janice; Cowden, John
Cc: Powers, Christina
Subject: iAs MOA lit search

Hi Ryan,

Thanks so much for your helpful insight during today's call discussing the mode of action lit search. Would you mind sending all of the keyword lists that you've tagged the MOA cluster with? I just want to double-check how they align and make sure I'm correctly identifying the lists that you received from John, myself and Janice.

Thanks!!
Christy

Christy Powers
Biologist
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Bohn, Brent

985

From: Turley, Audrey <Audrey.Turley@icfi.com>
Sent: Monday, July 28, 2014 1:30 PM
To: Powers, Christina

We just need to see the key word list!

986

Bohn, Brent

From: Lee, Janice
Sent: Monday, July 28, 2014 11:14 AM
To: Gift, Jeff; Kirrane, Ellen; Luben, Tom; Mendez Jr, William; Cowden, John; Sams, Reeder
Cc: Turley, Audrey; Blain, Robyn; Powers, Christina
Subject: 2010 arsenic noncancer draft with Appendices
Attachments: Arsenic_noncancer_09-09-2011.docx

Hi Jeff et al.,

Attached is the noncancer draft from 2010. The summary that Bill mentioned for the Kwok study is in Appendix D.

Janice

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Use of mode of action data to inform a dose–response assessment for bladder cancer following exposure to inorganic arsenic

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ABSTRACT

In the recent National Research Council report on conducting a dose–response assessment for inorganic arsenic, the committee remarked that mode of action data should be used, to the extent possible, to extrapolate below the observed range for epidemiological studies to inform the shape of the dose–response curve. Recent *in vitro* mode of action studies focused on understanding the development of bladder cancer following exposure to inorganic arsenic provide data to inform the dose–response curve. These *in vitro* data, combined with results of bladder cancer epidemiology studies, inform the dose–response curve in the low-dose region, and include values for both pharmacokinetic and pharmacodynamic variability. Integration of these data provides evidence of a range of concentrations of arsenic for which no effect on the bladder would be expected. Specifically, integration of these results suggest that arsenic exposures in the range of 7–43 ppb in drinking water are exceedingly unlikely to elicit changes leading to key events in the development of cancer or noncancer effects in bladder tissue. These findings are consistent with the lack of evidence for bladder cancer following chronic ingestion of arsenic water concentrations <100 ppb in epidemiological studies.

1. Introduction

A salient feature of the extensive environmental health arsenic literature is the large number of human observational studies available that describe both cancer and noncancer effects associated with environmental arsenic exposure whereas traditional standard rodent studies have been only moderately supportive in illustrating adverse effects that parallel those observed in humans. Epidemiology data in human populations exposed to arsenic for multiple generations provide clear evidence of cancer and noncancer effects at drinking water exposures above 100 ppb (Chen et al., 1986, 2010a, 2010b; IARC, 1987, 2004; NRC, 1999, 2001; Ferreccio et al., 2000; Karagas et al., 2001; Yuan et al., 2010). However, the potential for adverse effects at lower concentrations remains contentious due to the possible impact of exposure misclassification at low exposure levels as well as other possible confounders that include both genetic background and lifestyle factors (Bates et al., 1995; Guo et al., 1997; Lewis et al., 1999; Chiou et al., 2001; Steinmaus et al., 2003; Karagas et al., 2004; Lamm et al., 2004; Han et al., 2005; Baastrup et al., 2008; Meliker et al., 2010). Thus there is general agreement that the evidence for arsenic health effects is strong at high drinking water concentrations, but characteristics of response at drinking water exposure values below 100 ppb remain controversial. The lack of information available to characterize the dose–response curve below this concentration leads to difficulty in resolving what constitutes a "safe" level of arsenic exposure.

In conducting a cancer risk assessment under the latest regulatory guidelines (EPA, 2005), an understanding of the mode of action is critical for selecting the appropriate approach for low-dose extrapolation. For compounds, such as arsenic, a significant database regarding the mode of action for cancer development is available that may provide the ability for more complex approaches for low-dose extrapolation, such as the development and application of a biologically based dose–response model (Kitchin and Conolly, 2010). This type of model would integrate all of the quantitative information relevant for estimating an acceptable concentration. However, because this approach requires a significant amount of data to both develop the model and then independently confirm it with extrinsic data sets, the likelihood that such an extensive database will be available for

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0887-2333/

inorganic arsenic in a timeframe that would assist current quantitative risk assessments is unlikely. Therefore, it becomes critical to develop an approach that relies solely upon the currently available scientific data (*in vivo*, *in vitro* and epidemiological) for arsenic compounds to determine the dose–response curve for effects from arsenic exposure.

Although considerable information on mode of action is available for inorganic arsenic (Li and Rossman, 1989; Yager and Wiencke, 1993, 1994; Snow et al., 2005; Wei et al., 2005; Cohen et al., 2006, 2007; Qin et al., 2008; Straif et al., 2009; EFSA, 2009; Gentry et al., 2010), these data have not been integrated into a harmonized dose–response assessment approach. It is important to note that the available data do not suggest arsenic is a direct-acting mutagen (ATSDR, 2007; Klein et al., 2007; Kitchin and Wallace, 2008; EFSA, 2009) but that it does react directly with cellular proteins (Kitchin and Wallace, 2005, 2008; Benton et al., 2011; Zhou et al., 2011).

In the recent review of the current United States Environmental Protection Agency (EPA) draft Integrated Risk Information System (IRIS) assessment for arsenic (NRC, 2013); the Committee noted that epidemiologic data are expected to serve as the basis for the dose response analyses for inorganic arsenic performed for most end points. Importantly, the Committee further noted that should the data in the range of observation be inadequate for developing risk estimates that meet EPA's needs, mode-of-action data should be used to the extent possible to extrapolate below the observed range. The Committee further commented on the importance of understanding interhuman variability and asserted that mode of action data can be used to guide modeling qualitatively in the low dose region and also in considering susceptibility even if the mode of action cannot be firmly established.

Based on recent research related to genomic responses and cancer, it has been suggested that the dose–response assessment for cancer risk assessments could be based upon quantitation of molecular endpoints, or "bioindicators" of response, selected on the basis of their association with events that are known to be necessary to occur prior to the development of tumors (Preston, 2013). A critically important milestone in the use of mode of action data has also been reached with the demonstration that concentrations associated with changes in gene expression for selected compounds are in concordance with concentrations associated with apical endpoints (Thomas et al., 2013), and that transcription perturbation does not occur at significantly lower doses than apical responses.

A framework for a quantitative dose–response approach to define the shape of the dose–response curve in the low-dose region can thus be developed based on the foregoing concepts. Application of available arsenic health effects data, combined with a number of scientific tools (e.g., genomics, toxicology, human pharmacokinetics) provides for an approach as an alternative to the assumed default linear extrapolation of effects at low exposures derived solely from effects observed at considerably higher arsenic exposure concentrations. The application of these data then allows for the identification of a point of departure (POD) that can then be integrated with known pharmacokinetic and pharmacodynamic variability to provide quantitative information designating the lowest concentrations at which arsenic begins to perturb biological pathways.

2. Methods

2.1. Identification of a point of departure

A series of studies has been conducted to provide sequential illumination of important aspects of arsenic's mode of action at the genomic molecular level at relatively low doses (Gentry et al., 2010; Clewell et al., 2011; Yager et al., 2013a, 2013b). Arsenic is a known human bladder carcinogen at drinking water exposures >100 ppb (Chen et al., 1988; Cuzick et al., 1992; Chiou et al., 1995; Tsuda et al., 1995; Hopenhayn-Rich et al., 1996; Steinmaus et al., 2003) and so this internal organ was chosen as the first target organ upon which to conduct focused mode of action research. This research has focused not only on genomic changes following short-term exposures to inorganic arsenic and its major metabolites, but also changes in these cellular genomic alterations with time. The research was initiated with a critical review of the available *in vitro* genomic literature to integrate the available dose–response information in the low concentration region (Fig. 1). Studies were then designed to provide important low exposure (dose) information about changes at the cellular level across a gradient of low exposures and across time at those doses. A parallel study is currently underway focused on human lung cells, as the lung is also an internal target organ for cancer following high arsenic exposures by either inhalation or ingestion (Welch et al., 1982; Enterline et al., 1987; Ferreccio et al., 2000; Chen et al., 2004; Mostafa et al., 2008; Chen et al., 2011).

2.2. Critical review of arsenic in vitro literature (Gentry et al., 2010)

An initial comprehensive literature review was conducted to identify information on gene expression or protein expression changes related to specific multiple inorganic arsenic exposure concentrations in a variety of mammalian cells in culture (that is, experiments fundamentally conducted in the test tube) (Gentry et al., 2010). Results from three principal mammalian cell types were grouped by category: primary cells (normal cells); immortalized cells (cells stimulated to grow for long periods in culture by insertion of portions of a virus into the cells or by other means); or tumor cells (cells derived from human tumors that will also grow in culture for long periods of time). Changes in gene or protein expression in the treated cells were grouped by functional category (for example, those representing oxidative stress, proteotoxicity, inflammation, cell cycle checkpoint control, DNA repair activities, and cell survival or cell death). For each gene or protein expression change, the lowest concentration associated with a significant change was identified, and then comparison of the changes by functional category and dose was conducted. A principal finding from this review of results in cells from tissues in a number of mammalian species was that the mode of action included inhibition of repair processes in the cell. In addition, the gene changes observed across different mammalian cells and cells from different organs exhibited a transition in response from one of adaptation in response to arsenic exposure at low concentrations transitioning to gene expression changes that reflect frankly toxic effects at higher concentrations (Fig. 2).

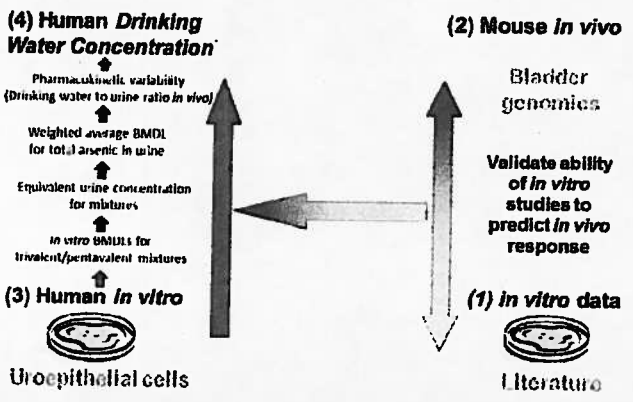

Fig. 1. Evaluating mode of action: Inorganic arsenic.

Please cite this article in press as: Gentry, P.R., et al. Use of mode of action data to inform a dose–response assessment for bladder cancer following exposure to inorganic arsenic. Toxicol. in Vitro (2014), http://dx.doi.org/10.1016/j.tiv.2014.05.011

2.3. Mouse in vivo study (Clewell et al., 2011)

An *in vivo* sub-chronic (90 day exposure) study was then conducted in groups of mice exposed to inorganic arsenic in drinking water at concentrations of 0, 0.5, 2, 10, or 50 mg/L (Clewell et al., 2011). Analyses of gene expression changes in the bladder were conducted at 1 and 12 weeks after the initiation of exposure. Changes in the direction of gene expression (increased or decreased) and expression of relatively different genes were noted between concentrations and between 1 week and 12 weeks (Fig. 3). The genomic results in the mouse bladder were overall consistent with the findings from the literature review (Gentry et al., 2010). The functional categories of affected genes provided no evidence of a linear exposure–response across the doses. In fact, there was strong evidence of a concentration-dependent transition at a drinking water concentration of 2 mg/L which is equivalent to an inorganic arsenic concentration of 0.1 μM in the urine as determined by analysis of urinary arsenic species in these exposed animals.

2.4. Human in vitro studies (Yager et al., 2013a, 2013b)

Studies have been conducted *in vitro* by Yager et al. (2013a, 2013b) in primary human uroepithelial cells from multiple normal individuals to investigate the mode of action for bladder cancer following exposure to inorganic arsenic compounds across a wide range of concentrations. Differentiated cells were treated with mixtures of inorganic arsenic and its pentavalent or trivalent metabolites at total arsenic concentrations ranging from 0.06 μM to 18 μM. Following arsenic exposures, results from human primary urothelial cell gene expression microarray analyses and genomic pathway investigations are consistent with data on other chemical stressors, in that there appears to be a transition from an adaptive state at low concentrations to an impaired state at higher concentrations (Snow et al., 2005; West and Marnett, 2005; Gilmour et al., 2006). Benchmark dose modeling of results from these *in vitro* studies identified a range of concentrations at which this transition occurs in human bladder target cells, with trivalent arsenic mixtures exhibiting slightly more potency than mixtures containing pentavalent species as expected (Table 1). This range of concentrations also represents potential pharmacodynamic variability since the study relied upon samples of bladder tissue from multiple individuals.

Benchmark dose analyses on gene expression results in this study) (Table 1) indicate benchmark dose lower confidence limits (BMDLs) 0.09–0.58 μM for total arsenic in trivalent arsenical mixtures; and 0.35–1.7 μM for total arsenic in pentavalent mixtures. Lower BMDLs for trivalent versus pentavalent mixtures is consistent with the published literature (Wang et al., 2007; Nascimento et al., 2008; Vahidnia et al., 2008) that suggests trivalent arsenic

	0.01 μM[3]	0.1 μM[4]	1.0 μM[6]	10 μM[15]	100 μM[20]
Oxidative Stress	Trx Reductase[2] SOD 1[2] NQO1[2]		HO-1[7] TPX-11[8] AP-1*[9]		MT-1[21] MT-2[21]
Inflammation	COX-2[2]			IL-8[14]	
Proteotoxicity	HSP-32[3]		HSP-32[9]	HSP-75[17]	HSP-60[22] HSP-27[9]
Proliferation	FGFR4[2]	Fos*[3] Myc*[3]	VEGF[10] p70*[11] Myc[12] ERK[13]	JNK3[18] Jun[9]	Jun[9]
DNA Repair	DDB2[2]	MSH5 APEX	AP-1[3]	GADD153[17]	GADD153[22]
Cell Cycle Control	p53[2]	p21[2] CDC25B[2]	p53**[16] p53[2]	p38[18] p21**[16] MDM-2**[16]	
Apoptosis	p53[2] ERG-1[2] p105[2] p65[2]	NF-kB*[5]	p53**[16] AP-1*[3] p53[2]	SRC*[19]	

Gene Expression: ☐ Decreases ☐ Increases
*Protein
**Notation for fibroblasts (14 day exposure)
NOTE: Empty cells do not indicate a lack of studies conducted at that concentration range, rather they indicate no statistically significant changes in up or down regulation of genes or proteins evaluated. Studies are categorized into specific concentrations. The actual range of concentrations is provided in footnotes.

[1]Administration of 0.005 to 0.01 μM included
[2](Hamadeh et al. 2002)
[3](Parrish et al. 1999)
[4]Administration of 0.1 to 0.5 μM included
[5](Liao et al. 2004)
[6]Administration of 1.0 to 2.5 μM included
[7](Sturlan et al. 2003)
[8](Hiarno et al. 2003)
[9](Wijeweera et al. 2001)
[10](Kao et al. 2003)
[11](Wang and Proud 1997)
[12](Shimizu et al. 1998)
[13](Lau et al. 2004b)
[14](Yih and Lee 2000)
[15](Administration of 6 to 13 μM included
[16](Jaspers et al. 1999)
[17](Rea et al. 2003)
[18](Barchowsky et al. 1999b)
[20]Administration of 30 to 100 μM included [21](Garrett et al. 2001)
[22](Mengesdorf et al. 2002)

Fig. 2. Dose–response relationships for the *in vitro* effects of arsenic – transition from adaptive responses to toxicity between 0.1 and 1.0 μM (Gentry et al., 2010).

Please cite this article in press as: Gentry, P.R., et al. Use of mode of action data to inform a dose–response assessment for bladder cancer following exposure to inorganic arsenic. Toxicol. in Vitro (2014), http://dx.doi.org/10.1016/j.tiv.2014.05.011

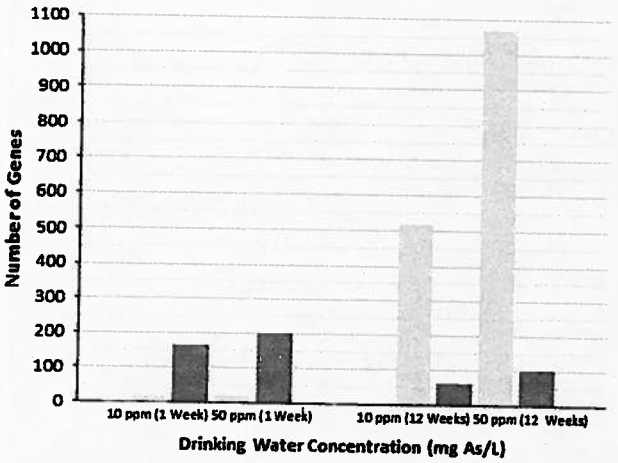

Fig. 3. Number of genes significantly down regulated (dark grey) or significantly upregulated (light grey) as a function of drinking water concentration at weeks 1 and 12 at 10 and 50 ppm (Clewell et al., 2011). Significance was defined as ±1.5-fold and q value <0.05.

species are more toxic than pentavalent arsenic species as previously mentioned.

Benchmark doses (BMDs) and BMDLs varied by an approximate factor of three across individuals, which is consistent with the default adjustment factor of 3 typically used for adjustment for interhuman pharmacodynamic variability (EPA, 1993; IPCS, 2005). These BMDLs represent "no effect" concentrations, at which no changes in gene expression were observed in response to arsenic exposure. Using an alternative statistical method for analysis, the authors were also able to confirm consistent no observed effect levels (NOELs) ranging from 0.18 μM to 1.8 μM total arsenic concentration for these same genes.

The foregoing study utilized 24 h *in vitro* treatment times. A follow-up study has been conducted with primary human uroepithelial cells in culture using a similar study protocol, but this time cells were treated for periods of up to 60 days (Yager et al., 2013b; manuscript in preparation). Results of serial genomic analyses conducted at 10, 20, 30, 40 and 60 days of exposure were consistent with previous results in that there was a general pattern of progression from cellular genomic pathways associated with inflammation, cell adhesion and growth regulation to pathways associated with DNA damage and apoptosis.

2.5. In vitro to in vivo extrapolation

Because concentrations of arsenic species administered in the *in vitro* studies were based on available information on the ratio of these species *in vivo* and conducted in primary bladder cells, extrapolation of the POD identified from the *in vitro* studies to *in vivo* can be readily conducted. These concentrations are consistent with ratios of trivalent and pentavalent urinary arsenic species reported in epidemiological studies (inorganic arsenic (iAs): monomethlarsonous acid (MMA): dimethylarsinate (DMA) ratios of 1:1:4) (Del Razo et al., 1997; Mandal et al., 2001). Concentrations from *in vitro* studies, found in Table 2, (Yager et al., 2013a) can be conservatively assumed to represent the concentrations in the urine that would be in contact with the urinary bladder. Based on this idea, extrapolation of *in vitro* to *in vivo* urinary concentration PODs can be carried out.

$$\text{In Vitro Concentration } (\mu M) \times \text{Molecular Weight} = \text{Urine Concentration } (\mu g/L)$$

2.6. Contribution of trivalent and pentavalent species

A review of the literature was conducted to identify studies from human populations characterizing the fraction of arsenic species in the urine of individuals exposed to drinking water containing arsenic. Since the *in vitro* testing was conducted with arsenic mixtures containing trivalent or pentavalent species separately, but in the same proportions as are present as metabolites in the urine of humans exposed to arsenic, the NOELs or PODs for trivalent or pentavalent arsenic are to be "weighted" to capture the potential contribution from both species in the proportion as they are present *in vivo*.

2.7. Pharmacokinetic variability

A literature review was conducted to identify studies from populations to provide data to characterize potential interhuman pharmacokinetic variability. The search was focused on studies providing both total arsenic concentrations in the urine and associated drinking water concentrations in order to estimate drinking water to urine ratios. This allows for the estimation of drinking water concentrations associated with the POD, expressed in urinary concentration from the *in vitro* data, without the application of a complex model. Consideration of the ranges in the ratios also provides an estimate of a range of potential drinking water concentrations associated with the POD, characterizing interhuman variability in pharmacokinetics.

2.8. Estimation of an acceptable drinking water concentration

Using the results of the *in vitro* gene expression studies, in combination with the results of the information identified in the available published epidemiological literature, an acceptable drinking water concentration was estimated. This drinking water concentration was estimated based on the estimated range of *in vitro* NOELs, which provide an estimated of interhuman variability in pharmacodynamics. In addition, data from the epidemiological literature that provided information to estimate interhuman variability in pharmacokinetics was considered. The resulting *in vitro* to *in vivo* extrapolation identifies a range of estimated drinking water concentrations that reflect arsenic concentrations at which no effect on cellular genomic pathways in human bladder cells *in vivo* would be expected.

3. Results

3.1. Points of departure from in vitro data

The genomic response study conducted by Yager et al. (2013a) showed significant changes in expression of the most common genes affected across individuals at concentrations in the range of 0.1–1.0 μM total arsenic for both trivalent and pentavalent arsenical mixtures. The range of BMDLs determined in this study represents a range of NOELs at the cellular level. These are concentrations at which no impact on cellular genomic expression pathways were seen to occur and also take into account interhuman variability in response. It is further inferred that the NOELs are not restricted solely to cancer effects, but rather that they provide concentration ranges for which NO impact of arsenic exposure would be expected. The NOELs thus represent PODs that can be used for estimation of acceptable drinking water concentrations in the low exposure portion of the dose–response curve (e.g., ≤100 ppb arsenic in drinking water) at which significant risk for bladder cancer has not been observed in epidemiological studies. Thus the range of NOELs are put forward here to be applied in a risk

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Table 1
Comparison of genomic benchmark doses (NOELs) in human bladder cells (Yager et al., 2013a).

Gene name	Gene probe Id	Description	Trivalent			Pentavalent		
			Number of subjects expressing the gene/total	BMD range (μM)	BMDL range (μM)	Number of subjects expressing the gene/total	BMD range (μM)	BMDL range (μM)
HMOX1	203665_at	Oxidative stress response	10/10	0.13–0.50	0.09–0.33	3/5	1.6–2.7	1.1–1.7
FKBP5	224840_at	Protein folding	9/10	0.36–0.92	0.24–0.58	4/5	1.0–2.2	0.66–1.4
TXNRD1	201266_at	Thioredoxin reductace	9/10	0.32–0.75	0.21–0.48	3/5	2.3–2.6	1.5–1.7
MT1E	212859_x_at	Metallothionine regulation	8/10	0.24–0.77	0.16–0.49	4/5	0.53–1.7	0.35–1.1
DDB2	203409_at	DNA damage sensing	8/10	0.30–0.88	0.20–0.56	4/5	0.67–2.3	0.44–1.5
TXN	208864_s_at	Thioredoxin	8/10	0.26–0.76	0.17–0.48	5/5	2.0–2.4	1.3–1.5
LGALS8	208933_s_at 208934_s_at 208935_s_at 208936_x_at 210731_s_at 210732_s_at	Cell adhesion, growth regulation	10/10	0.16–0.92	0.11–0.58	4/5	1.0–2.3	0.69–0.15
THBD	203888_at 203887_s_at 237252_at	Immune response	8/10	0.32–0.90	0.20–0.57	3/5	0.55–2.7	0.37–1.7

assessment as a range of PODs for determining concentrations for which no impacts on biological pathways in the bladder would be expected.

3.2. In vitro to in vivo extrapolation

Because the arsenic mixtures administered in the *in vitro* studies represent the mixtures present in the urine from epidemiological studies (Del Razo et al., 1997), it can be conservatively assumed that the *in vitro* concentrations described in Yager et al. (2013a) are equivalent to those present in the urine *in vivo*. This then requires a simple conversion of the micromolar concentrations to "equivalent" urine concentrations, adjusting by the molecular weight. The resulting *in vivo* "equivalent" urine concentrations for the PODs determined from the *in vitro* data are 6.5–43.5 μg/l for the trivalent mixture and 26.25–127.5 μg/l for the pentavalent mixture.

3.3. Contribution of trivalent and pentavalent species

The literature search identified a study conducted by Mandal et al. (2001) in which a method was developed to estimate the contribution of trivalent and pentavalent species in the urine. Samples of drinking water ($N = 78$) and urine ($N = 428$) were obtained from four groups (A–D) in four arsenic-affected blocks of three arsenic-affected districts in India. Mean drinking water concentrations ranged from <3 to 248 ppb (Table 3). Based on the percentages from these multiple areas, the trivalent species (arsenite + MMAiii + DMAiii) represent approximately 30% of the total arsenic and the pentavalent species (arsenate + MMAv + DMAv) represent approximately 75%.

These data provide an estimate of the contribution of trivalent and pentavalent species in an approximate 1:2.5 ratio. Adjusting the contribution of the BMDLs by this ratio results in a weighted average range of BMDLs of 21–104 μg/l, representing a POD expressed in sum (total iAs (iAsIII + iAsV) + total MMA (MMAIII + MMA V) + total DMA (DMAIII + DMAV) of relevant arsenic species in urine.

$$\frac{\text{Pentavalent BMDL} \times 0.75 + \text{Trivalent BmDL} \times 0.3}{105} = \text{Weighted BMDL}$$

The lower end of the range of BMDLs (21 μg/l) is consistent with a Biomonitoring Equivalent (BE) POD for noncancer effects of 19.3 μg arsenic/L urine estimated by Hays et al. (2010) for the USEPA Reference Dose (RfD) and the ATSDR Minimal Risk Level (MRL). A BE is a concentration of a chemical in a biological medium (blood, urine or other medium) that is consistent with an existing health-based exposure guidance value, such as an RfD. Existing chemical-specific pharmacokinetic data are used to estimate biomarker concentrations that are consistent with the POD used in the derivation of an exposure guidance value.

3.4. Pharmacokinetic variability

The literature search identified multiple studies conducted in various areas in Mexico and in Canada with a wide range of exposure to arsenic concentrations in drinking water (Del Razo et al., 1997, 2011; Valenzuela et al., 2005; Normandin et al., 2013). These studies provided mean and range of urinary sum of arsenic metabolite species concentrations and the associated mean and range of drinking water concentrations. Using this information, the mean and ranges of arsenic drinking water to arsenic urine concentration ratios were calculated (Table 4).

These data suggest a range of drinking water to urine concentration ratio for sum of arsenic in the urine ranging from 0.33 to 2.1. The low arsenic drinking water concentration group (≪1 ppb) in the Normandin et al. (2013) study results in very low drinking water to urine ratios, as low as 0.01. However, comparison of the urinary arsenic concentrations to those in the drinking water indicate that these urinary arsenic concentrations are unlikely to be attributable to arsenic in drinking water alone, but likely arise from an alternate source of arsenic, such as the diet (Torres-Escribanos et al., 2008; Meliker et al., 2010; Xue et al., 2010; Jackson et al., 2012). Therefore, these values were not relied upon to characterize pharmacokinetic variability resulting from exposure in drinking water. The range of variability associated with drinking water ingestion also provides information on the interhuman variability in pharmacokinetics, suggesting a factor of approximately 6, which is double the default factor of 3 typically used in human health risk assessments for interhuman variability in pharmacokinetics (IPCS, 2005; EPA, 1993).

Adjustment of the lowest BMDL or POD for the sum of arsenic in the urine (21 μg/l) by this ratio, providing an estimate of in phar-

Table 2
Arsenic *in vitro* 24 h treatment protocols (Yager et al., 2013a).

Treatment	iAs^{III} (μM)	MMA^{V} (μM)	DMA^{V} (μM)	Total mixture (μM)
(a) Arsenite plus pentavalent metabolites				
Control	0	0	0	0
1	0.01	0.01	0.04	0.06
2	0.1	0.1	0.4	0.6
3	0.3	0.3	1.2	1.8
4	1	1	4	6
5	3	3	12	18
	iAs^{III} (μM)	MMA^{III} (μM)	DMA^{III} (μM)	Total mixture (μM)
(b) Arsenite plus trivalent metabolites				
Control	0	0	0	0
1	0.01	0.01	0.04	0.06
2	0.03	0.03	0.12	0.18
3	0.1	0.1	0.4	0.6
4	0.3	0.3	1.2	1.8
5	1	1	4	6

Table 3
Percent of total urinary arsenic concentrations for multiple arsenic species from arsenic affected districts in India (Mandal et al., 2001).

	MMAiii	DMAiii	MMAv	DMAv	Arsenite	Arsenate
Percent in urine						
Group A	4	19	8	45	14	10
Group B	4	11	10	46	13	13
Group C	5	21	10	44	13	8
Group D	2	4	11	74	8	2
Mean	4	14	10	52	12	8

macokinetic variability, results in an estimated range of the lowest estimated drinking water concentrations associated with the lowest estimated NOEL equivalent. The range includes the variability in response measured across individuals. The resulting range of estimated drinking water concentrations would be approximately 7–43 μg/l.

$$\text{Ratio} = \frac{\text{Drinking water concentration (μg/L)}}{\text{Urine concentration (μg/L)}}.$$

3.5. Estimation of an acceptable drinking water concentration

Therefore, based on *in vitro* results, together with observed arsenic drinking water: urinary arsenic ratios, and taking into consideration available data on interhuman variability in both pharmacokinetics and pharmacodynamics, a range of drinking water concentrations at which no effects in the bladder would be expected is 7–43 μg/l.

4. Discussion

Recent *in vivo* and *in vitro* studies have been conducted to further elucidate mode of action and genomic dose-dependent transitions for arsenic carcinogenicity, focusing on analyzing changes in gene expression in bladder tissue over a wide range of biologically plausible concentrations of urinary arsenic species (Clewell et al., 2011; Yager et al., 2013a, 2013b). It is recognized that evidence of arsenic carcinogenicity has been reported in other tissues and that extension of this research to other tissues such as lung and liver are desirable in order to determine the existence and nature of dose- and time-dependent transition points in other target tissues. The comprehensive *in vitro* literature review by Gentry et al. (2010) found that the genomic response to arsenic was not tissue specific and suggested the existence of these same types of transitions for other mammalian tissues, however, additional experimental work is necessary to confirm these observations.

This research to investigate mode of action of arsenic mixtures in the bladder also provides a unique opportunity for the development of an initial approach for the application of these data in a risk assessment. The technology relied upon for this research (i.e., gene-expression microarrays, high-throughput cell-based assays) provides a new method for assessing the impact of chemical exposures on the processes that control and modulate biological systems (Rhomberg, 2010). The use of these data is critical for achieving the visions outlined by the National Research Council (NRC) (2007) to move away from animal testing toward a fundamental understanding of the impact of chemical exposure on biological systems. The use of these data is also consistent with the recent recommendations from the NRC (2013) for inorganic arsenic, suggesting the application of these types of data to define the shape of the dose–response curve at concentrations lower than those reported in epidemiological studies.

This study incorporates *in vitro* results into the risk assessment paradigm, however, as illustrated herein, integration of *in vitro* results with *in vivo* information as was done in this study is critical. The estimated range of acceptable drinking water concentrations based on the *in vitro* results that would be expected to result in no effects on the bladder is approximately 7–43 μg/l. This information represents an original effort to define the shape of the dose–response curve below drinking water concentrations of approximately 100 ppb, where there remains debate on the evidence related to bladder cancer following drinking water exposure to inorganic arsenic.

Table 4
Estimated arsenic drinking water to arsenic urine concentration ratios from multiple epidemiological studies.

Reference	Sum of urinary arsenic (μg/g creatinine)			Sum of urinary arsenic (μg/l)			Total arsenic drinking water concentration (μg/l)			Drinking water to urine ratio		
	Mean	Min	Max	Mean/ median	Min	Max	Mean/ median	Min	Max	Mean	Min	Max
Del Razo et al. (1997) (control)	19.5	14.8	26.7	24.5[a]	14.1[a]	41.7[a]	25	20	40	1.0	1.42	0.96
Del Razo et al. (1997) (exposed)	543.8	429.3	689.4	781.9[a]	498.8[a]	1181.6[a]	415	396	470	0.53	0.79	0.40
Del Razo et al. (2011)				41.2	2.3	233.7	42.9	3.1	215.2	1.0	1.3	0.92
Valenzuela et al. (2005) (total population)	84.85	9.1	1398.1	50.5[b]	0.96[b]	4515.9[b]	77.8	1	1504	1.54	1.05	0.33
Valenzuela et al. (2005) (exposed without skin lesions)	116	61.2	371.7	69.0[b]	36.4[b]	221.2[b]						
Normandin et al. (2013) (low exposure group)				5.31	2.20	24.9	0.13	<0.02	0.88	0.02	0.01	0.04
Normandin et al. (2013) (mid exposure group)				7.01	2.68	18.9	2.7	1.0	9.8	0.39	0.37	0.52
Normandin et al. (2013) (high exposure group)				18.9	5.33	108	36	11	140	1.9	2.1	1.3

[a] Estimated based on the reported mean creatinine of 1438 μg/l and a range of 1162–1714 μg/l.
[b] Estimated based on the reported mean creatinine of 595 mg/L and a range of 105–3230 mg/L.

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Table 5
Summary of bladder cancer epidemiology studies and exposure to arsenic in drinking water.[a]

	Reference	Study type	Exposure metric	Outcome measure	Number of cases/controls or population at risk	Arsenic (μg/l) drinking water concentration[b]	Geographic area
1	Guo et al. (1997)	Ecological study	Water [As] estimates	Incident bladder cancer cases	1972 cases in 243 Taiwan townships containing a total population of 11.4 million	<330 μg/l	Taiwan
2	Chiou et al. (2001)	Cohort study	Water [As] estimates	Incident transitional cell bladder cancer cases	11 cases/8102 population at risk	≤100 μg/l	NE Taiwan
3	Chen et al. (2010a, 2010b)	Cohort study	Water [As] estimates	Incident urothelial carcinoma cases	36 cases/8086 population at risk	<100 μg/l (exposure range 0.15–3000 μg/l)	NE Taiwan
4	Bates et al. (1995)	Case-control study	Water [As] estimates	Incident bladder cancer cases	71 cases/160 controls	0.5–160 μg/l	Utah
5	Lewis et al. (1999)	Cohort study	Water [As] estimates	Bladder cancer mortality (SMR)	Male SMR = 0.42 Female SMR = 0.81	Mean 5.0 μg/l 14–166 μg/l Median and weighted mean per county is 100 μg/l	Utah
6	Steinmaus et al. (2003)	Case-control study	Water [As] estimates	Incident bladder cancer cases	5 bladder cancer cases observed/9 expected in a population at risk of 4058 181(never smokers) cases/328 controls	<80 μg/day for <30 yrs	Nevada/ California
7	Karagas et al. (2004)	Case-control study	Toenail [As]	Incident transitional cell bladder cancer cases	383 cases/641 controls	Authors estimate: ≤50 μg/l	New Hampshire
8	Lamm et al. (2004)	Ecological study	Ground water [As] estimates (USGS) in 133 counties in 26 states of the contiguous United States	Lifetime (75 yrs) bladder cancer mortality in white males	4537 observed white male bladder cancer deaths/4820 expected in a population at risk of 2,498,185. 75 million Person-Years of observation	<60 μg/l Median county values 3–60 μg/l 82% of population at 3–5 μg/l	United States
9	Han et al. (2009)	Ecological study	Ground water [As] estimates	Bladder cancer cases diagnosed 1991–2005 in all 44 counties of the state with a total population of 1.2 million	Low As <2 μg/l 960 cases/354,970 $N = 23$ counties Med As 2–<10 μg/l $N = 16$ counties 1895 cases/640,588 High As >10 μg/l $N = 5$ counties 675 cases/220,728	No increased cancer risk at any level tested <2 to >10 μg/l	Idaho
10	Meliker et al. (2010)	Case-control study	Water [As] estimates	Incident urinary bladder cancer cases	411 cases/566 controls drawn from 11 counties with a total population of 260,000	≤10 μg/l	SE Michigan
11	Baastrup et al. (2008)	Cohort study	Water [As] estimates	Incident bladder cancer cases	214 cases/57,053 population at risk	25.3 μg/l max Mean 1.2 μg/l Median 0.7 μg/l	Denmark

[a] Tabled studies are restricted to those performed in US and European populations in which arsenic in drinking water values are ≤200 μg/l and studies from Taiwan in which arsenic in drinking water values are ≤300 μg/l.
[b] Estimated arsenic drinking water concentration which no significant increase in bladder cancer was observed.

A critical review of epidemiology studies that provide adequate exposure information, specifically at low drinking water concentrations (≤300 ppb) of arsenic, and also investigate the relationship between exposure to arsenic and bladder cancer, was conducted (Table 5) (Gentry et al., 2014). There is a lack of strong evidence for the incidence of bladder cancer from these studies, consistent with the results from recent meta-analyses.

Mink et al. (2008) conducted a meta-analysis of low-level (<100–200 μg/l) arsenic in drinking water and bladder cancer epidemiology studies. Heterogeneity across studies, and study design and sample size issues were examined in eight case-control and cohort studies that met inclusion criteria. The authors concluded that low-level arsenic exposure alone was not shown to be an independent risk factor for bladder cancer across these eight studies. In a recent updated meta-analysis (Tsuji et al., 2013), nine case-control and cohort studies were included. Consistent with the original findings, no significant association between low-level arsenic exposure and bladder cancer was observed (RR = 1.07; 95% CI = 0.95–1.26; p value for heterogeneity = 0.54). Therefore, the estimated range of drinking water concentrations associated with no potential effects on the bladder relying upon *in vitro* results appears consistent with the available data from studies conducted in human populations.

The range of estimated total arsenic urinary concentrations that would be associated with no effects on the bladder based on the *in vitro* results (21–104 μg/l) also appears to be consistent with total arsenic urinary concentrations reported in control or reference populations reporting no effects of arsenic exposure. In studies conducted by Del Razo et al. (1997) and Valenzuela et al. (2005), control populations were evaluated in which no signs of arsenicism or skin lesions were noted. The total arsenic urinary concentrations reported in these studies ranged from 5 to 63 μg/l. In addition, Del Razo et al. (1997) noted sum of arsenic urinary concentrations from 4 other control populations, with no effects of arsenic (Smith et al., 1977; Farmer and Johnson, 1990; Yamauchi et al., 1989; Del Razo et al., 1994) that ranged from 4.4 to 50.1 μg/l. In a recent study conducted in Vietnam (Agusa et al., 2013), the range of the sum of arsenic species in the urine, adjusted for creatinine, in the reference village (4–118 μg/g creatinine) were comparable to the concentrations in the Del Razo et al. (1997) and Valenzuela et al. (2005) control populations or those with no signs of arsenicism (14.8–371.7 μg/g creatinine) (Table 4). In addition, they were comparable with the urinary arsenic concentrations reported by Valenzuela et al. (2005) for those exposed individuals for which no effects of arsenic were observed (Table 4). Therefore, reliance upon the low end of the range of estimated total arsenic urinary concentrations associated with the NOEL from the *in vitro* data (21 μg/l) is consistent with total urinary arsenic concentrations from "control" populations who by definition have no untoward health effects associated with arsenic exposure.

In the Normandin et al. (2013) study, an analysis was also conducted to evaluate the presence of 8-hydroxy-2′-deoxyguanosine (8-OHdG) in the urine. 8-OHdG is a sensitive marker of DNA damage resulting from oxidative stress. Studies conducted by Yamauchi et al. (2004) and Fujino et al. (2005) have demonstrated increases in 8-OHdG levels in the urine of individuals following chronic consumption of drinking water containing >100 μg/l arsenic. In the Normandin et al. (2013) study, there was no association observed between urinary 8-OHdG levels and drinking water intake of arsenic (As) or hair, nail, or urinary exposure biomarker levels. The authors concluded that at these low concentrations (≤140 μg/l), a lack of association suggests that there is no significant indication of impending early toxic effects of arsenic exposure. These results are consistent with results presented by Burgess et al. (2007) in which no significant association between water arsenic exposure <40 μg/l and urinary 8-OHdG levels were observed.

In conclusion, Integration of the available *in vivo*, *in vitro*, pharmacokinetic and epidemiological evidence support an acceptable arsenic concentration in drinking water below 100 ppb, with the evidence from *in vitro* studies suggesting this acceptable concentration is in the range of 7–43 μg/l. As noted previously, additional work in the lung is ongoing by the study authors to determine if a similar threshold for arsenic effects can be determined for other target organs. It is important to note that this acceptable concentration should be protective for both cancer and noncancer effects in the bladder as the estimate is based on a NOEL for *any* effect on bladder cells. This provides an estimate of an acceptable "no effect" exposure level for arsenic in drinking water. The *in vitro* results suggest no impact on biological pathways in this range of exposure concentrations.

While this assessment represents an initial estimate based on *in vitro* results and an uncomplicated approach for the consideration of interhuman pharmacokinetic variability, pharmacokinetic models, such as those developed by El-Masri and Kenyon (2008) and Mann et al. (1996a, 1996b) could be used to further refine the estimated acceptable drinking water concentrations. These models may well assist in the estimation of exposure concentrations that could result in the bladder/urine concentrations of arsenic metabolites that have been reported in human populations (Sun et al., 2007; Kile et al., 2009; Fillol et al., 2010; Rivera-Nunez et al., 2012). However, it is critical that exposures in populations be characterized as accurately as possible. Exposure misclassification in epidemiology studies, particularly at arsenic drinking water concentrations below 100 ppb, has been conventionally asserted to result nearly exclusively in a trend toward the null or in observing no health effects at these levels of exposure with the implication that there could still exist "unobserved" health effects. Crump (2005) has convincingly demonstrated, however, that exposure misclassification in epidemiology studies transforms an exposure response relationship in the direction toward supralinear (i.e., tends to linearize a sublinear dose–response curve). Thus, the repetitious sole application of epidemiological methods to a wide range of human populations has been unable to satisfactorily resolve this issue.

The application of an integrated approach is consistent with the need expressed by both regulatory bodies and the scientific community to harmonize risk assessments for cancer and noncancer endpoints. The significance of the integration of approaches for health effects in general have been reported by previous investigators (Bukowski and Lewis, 2004; Clewell and Crump, 2005), including implications for cost–benefit and risk assessment for inorganic arsenic.

This study relies upon mode of action results from *in vitro* studies at biologically plausible arsenic concentrations and uses human genome-wide gene expression and pathway endpoints that are relevant for both noncancer and cancer endpoints In harmonizing mode of action results from *in vitro* studies in human primary cells with observational data from epidemiology studies, this study is the first to quantitatively estimate a concentration range of arsenic in drinking water that is highly unlikely to induce changes in human gene expression or perturbations in pathways that lead to key events in the progression to frank cancer or noncancer endpoints.

Conflict of Interest

The authors declare that there are no conflicts of interest. Q3

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Bohn, Brent 993

From: Philpott, Olivia
Sent: Thursday, July 24, 2014 10:20 AM
To: Powers, Christina
Subject: RE: Conference line request: Friday, 7/25 10:30-11:30 a.m.

Hi Christy,
Your request for the conference line is scheduled.

Regards

Olivia Philpott
Information Management Technician / NCBA
National Center for Environmental Assessment
Research Triangle Park Division
U.S. Protection Agency
Research Triangle Park, NC 27711
Phone: (919) 541-4915

From: Powers, Christina
Sent: Thursday, July 24, 2014 8:28 AM
To: Philpott, Olivia
Cc: Powers, Christina
Subject: Conference line request: Friday, 7/25 10:30-11:30 a.m.

Hi Olivia,

Is the conference line available tomorrow morning from 10:30-11:30 a.m.? If so, can you put my name down for it?

Thanks so much for your time and assistance!

Christy

Christy Powers
Biologist
National Center for Environmental Assessment (B 220-I)
Office of Research and Development
U.S. Environmental Protection Agency
Ann Arbor, MI

Tel: 734.214.4243
E-mail: powers.christina@epa.gov

994

Bohn, Brent

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Office of Research and Development
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Ann Arbor, MI

Tel: 734.214.4243
E-mail: powers.christina@epa.gov

995

Bohn, Brent

From: Powers, Christina
Sent: Thursday, July 24, 2014 8:25 AM
To: Lee, Janice; Gift, Jeff
Cc: Powers, Christina
Subject: RE: iAs Decision Tree for Data to Inform Dose-Response

Thanks Jeff and Janice! I'll send a calendar invite for 10:30 a.m. tomorrow morning.

Look forward to talking then but let me know if any questions come up in the interim.

Christy

From: Lee, Janice
Sent: Thursday, July 24, 2014 8:13 AM
To: Gift, Jeff; Powers, Christina
Subject: RE: iAs Decision Tree for Data to Inform Dose-Response

Thanks, Jeff.
Friday works better for me. Today I have a ton of meetings and an agency briefing for tba, so I won't have time today.
Tomorrow I am free 10:30-12 or anytime after 1.
If it works better, I can also meet Monday.

Janice

From: Gift, Jeff
Sent: Wednesday, July 23, 2014 5:32 PM
To: Powers, Christina
Cc: Lee, Janice
Subject: RE: iAs Decision Tree for Data to Inform Dose-Response

Yes, I can meet to discuss. Is Friday good for you guys? Or tomorrow morning, if I can study it by then.

Jeff Gift, Ph.D.
National Center for Environmental Assessment
EPA (B243-01)
RTP, NC 27711
919-541-4828
919-541-0245 (fax)
gift.jeff@epa.gov

From: Powers, Christina
Sent: Wednesday, July 23, 2014 11:48 AM
To: Gift, Jeff
Cc: Lee, Janice; Powers, Christina
Subject: iAs Decision Tree for Data to Inform Dose-Response

Hi Jeff,

The iAs AOP Team is developing a decision tree to communicate the value of mechanistic data in dose response analyses in the assessment. Based on some of our earlier discussions, I know you could offer a wealth of insight on the content of this decision tree. Do you have time to meet with Janice and I to discuss this week?

I'm attaching a draft of a similar decision tree that we developed for making a causality determination to provide an idea of the product we have in mind. For the dose-response decision tree we would use a different set of questions (green outline boxes) to guide when we look to human, animal, or mechanistic data.

As always, don't hesitate to contact me if any additional information would be helpful ahead of a discussion.

Thanks!
Christy

Christy Powers
Biologist
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Office of Research and Development
U.S. Environmental Protection Agency
Ann Arbor, MI

Tel: 734.214.4243
E-mail: powers.christina@epa.gov

Bohn, Brent

996

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Christy

Christy Powers

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Ann Arbor, MI

Tel: 734.214.4243
E-mail: powers.christina@epa.gov

Bohn, Brent

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Sent: Wednesday, July 23, 2014 11:48 AM
To: Gift, Jeff
Cc: Lee, Janice; Powers, Christina
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Thanks!
Christy

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Notice (If This Communication Regards a Contract): Nothing in this message shall be construed as a change to the price, schedule, or terms and conditions of the contract. If the receiver does construe it otherwise, please notify me immediately so that proper contract action can be initiated.

1000

Bohn, Brent

From: Lee, Janice
Sent: Wednesday, July 23, 2014 2:10 PM
To: Powers, Christina
Subject: VOI decision tree

Hey Christy,

Talked to Audrey about setting up a meeting to discuss MOA. Would you be comfortable sharing the draft decision tree at this point? She thought it might be useful to see at this point

Janice

Bohn, Brent 1002

From: Powers, Christina
Sent: Wednesday, July 23, 2014 11:48 AM
To: Gift, Jeff
Cc: Lee, Janice; Powers, Christina
Subject: iAs Decision Tree for Data to Inform Dose-Response
Attachments: 2014 07 22 iAs Mechanistic Data Vol Decision Tree_DRAFT.pptx

Hi Jeff,

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Thanks!
Christy

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Bohn, Brent 1011

From: Powers, Christina
Sent: Monday, July 21, 2014 11:20 AM
To: Lee, Janice
Cc: Powers, Christina
Subject: RE: aop abstract

Thanks Janice! Can you send the Word copy of the abstract that you shared with Jeff and the team? I'd like to start from that copy to revise/ check-in with the team on any additional revisions.

Hope you had a great weekend too!
Christy

-----Original Message-----
From: Lee, Janice
Sent: Monday, July 21, 2014 9:23 AM
To: Powers, Christina
Subject: FW: aop abstract

Hi Christy,

Here is Jeff's review. I can make the changes, but figured it might be easier for you to make them since it's going through clearance on your end.
Hope you had a nice weekend!

Janice

-----Original Message-----
From: EZTech_Printer [mailto:EZTek@epa.gov]
Sent: Monday, July 21, 2014 9:14 AM
To: Lee, Janice
Subject: aop abstract

Please open the attached document. This document was digitally sent to you using an HP Digital Sending device.

Bohn, Brent 1016

From: Gift, Jeff
Sent: Thursday, July 17, 2014 11:39 AM
To: Powers, Christina
Cc: Lee, Janice
Subject: Happy to review the abstract

Hi Christy,

Janice gave me the arsenic abstract you guys want reviewed. I should be able to finish the review this week.

Cheers,
Jeff

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